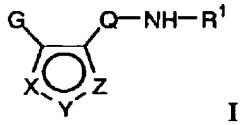
Atty. Docket No.: VPI/99-109 DIV US
Application No.: 10/779,532
Applicants: Green et al.

IN THE CLAIMS

Please replace all prior versions and listings of claims with the amended claims as follows:

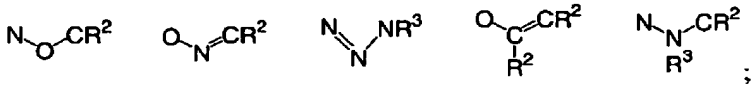
1. (Currently amended) A compound having the formula



I

wherein:

X-Y-Z is selected from one of the following:



;

R^1 is H, $CONH_2$, $T_{(n)}$-R, or $T_{(n)}$-Ar^2;

R is an aliphatic or substituted aliphatic group;

n is zero or one;

T is C(=O), CO_2, CONH, $S(O)_2$, $S(O)_2NH$, $COCH_2$ or CH_2;

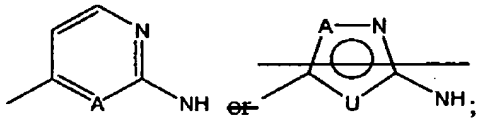
each R^2 is independently selected from hydrogen, -R, $-CH_2OR$, $-CH_2OH$, -CH=O, $-CH_2SR$, $-CH_2S(O)_2R$, $-CH_2(C=O)R$, $-CH_2CO_2R$, $-CH_2CO_2H$, $-CH_2CN$, $-CH_2NHR$, $-CH_2N(R)_2$, -CH=N-OR, -CH=NNHR, $-CH=NN(R)_2$, -CH=NNHCOR, $-CH=NNHCO_2R$, $-CH=NNHSO_2R$, -aryl, -substituted aryl, $-CH_2$(aryl), $-CH_2$(substituted aryl), $-CH_2NH_2$, $-CH_2NHCOR$, $-CH_2NHCONHR$, $-CH_2NHCON(R)_2$, $-CH_2NRCOR$, $-CH_2NHCO_2R$, $-CH_2CONHR$, $-CH_2CON(R)_2$, $-CH_2SO_2NH_2$, $-CH_2$(heterocyclyl), $-CH_2$(substituted heterocyclyl), -(heterocyclyl), or -(substituted heterocyclyl);

each R^3 is independently selected from hydrogen, R, COR, CO_2R or $S(O)_2R$;

G is R or Ar^1;

Ar^1 is aryl, substituted aryl, aralkyl, substituted aralkyl, heterocyclyl, or substituted heterocyclyl, wherein Ar^1 is optionally fused to a partially unsaturated or fully unsaturated five to seven membered ring containing zero to three heteroatoms;

Q-NH is



wherein the H of Q-NH is optionally replaced by R^3;

A is ~~N or~~ CR^3;

~~U is CR^3, O, S, or NR^3;~~

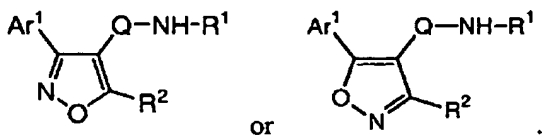
Ar^2 is aryl, substituted aryl, heterocyclyl or substituted heterocyclyl, wherein Ar^2 is optionally fused to a partially unsaturated or fully unsaturated five to seven membered ring containing zero to three heteroatoms;

wherein each substitutable carbon atom in Ar^2, including the fused ring when present, is optionally and independently substituted by halo, R, OR, SR, OH, NO_2, CN, NH_2, NHR, $N(R)_2$, NHCOR, NHCONHR, $NHCON(R)_2$, NRCOR, $NHCO_2R$, CO_2R, CO_2H, COR, CONHR, $CON(R)_2$, $S(O)_2R$, $SONH_2$, S(O)R, SO_2NHR, or $NHS(O)_2R$, and wherein each saturated carbon in the fused ring is further optionally and independently substituted by =O, =S, =NNHR, $=NNR_2$, =N-OR, =NNHCOR, $=NNHCO_2R$, $=NNHSO_2R$, or =NR; and

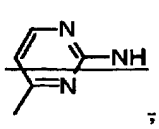
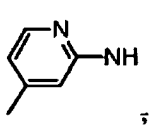
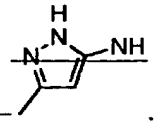
wherein each substitutable nitrogen atom in Ar^2 is optionally substituted by R, COR, $S(O)_2R$, or CO_2R.

2. (Original) The compound of claim 1 where G is Ar^1.

3. (Original) The compound of claim 2 having the formula



4. (Currently amended) The compound of claim 3 where Q-NH is ~~selected from:~~

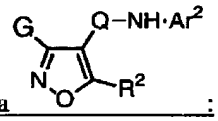

;

; ~~or~~

.

5. (Original) The compound of claim 4 where R^1 is alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, pyridinylalkyl, alkoxycycloalkyl, cycloalkyl, alkoxycarbonylcycloalkyl, hydroxycycloalkyl, Ar^2 or T-Ar^2 where T is C(=O).

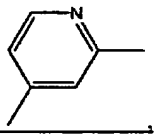
6. (Original) The compound of claim 5 where R^1 is cyclohexyl, cyclohexanol-4-yl, cyclohexanon-4-yl, 2-propan-1-ol, 2-methoxy-1-methylethyl, 3-butyryl alkyl ester, 2-pyridinyl-2-ethyl, or an optionally substituted phenyl, naphthyl, pyridyl, quinolinyl, thienyl or indanyl.

7. (Original) The compound of claim 6 where R^2 is an optionally substituted alkyl.

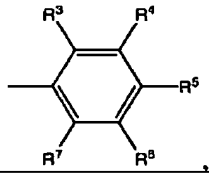
8. (Currently amended) A compound selected from the group consisting of ~~those listed in any of Tables 1-7.~~

(a) a compound of formula  :

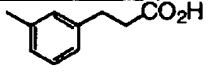
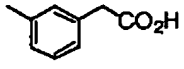
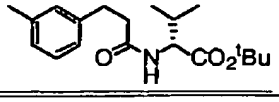
Atty. Docket No.: VPI/99-109 DIV US
Application No.: 10/779,532
Applicants: Green et al.

wherein Q is  ,

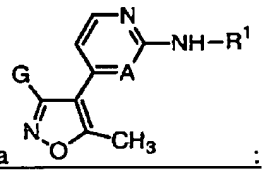
Ar^2 is R^1,

R^1 is  , and

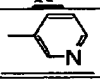
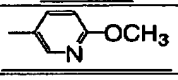
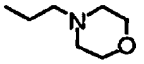
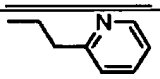
G, R^2, R^3, R^4, R^5, R^6 and R^7 are defined as

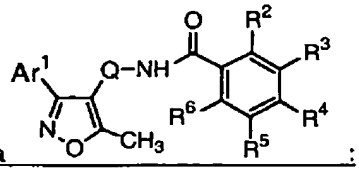
No.	G	R^2	R^3	R^4	R^5	R^6	R^7
IIA-16	Phenyl	Et	H	CN	H	H	H
IIA-17	Phenyl	Et	H	CO_2H	H	H	H
IIA-18	Phenyl	Me	H	F	H	H	H
IIA-19	Phenyl	Me	H	H	F	H	H
IIA-20	Phenyl	Me	H	H	COMe	H	H
IIA-21	Phenyl	Me	H	H	COPh	H	H
IIA-24	Phenyl	Me	H	H	$CONH_2$	H	H
IIA-40	Phenyl	Et	H	H	H	H	H
IIA-43	Phenyl	Me	H	CO_2H	H	H	H
IIA-47	Phenyl	Me	H	H	OMe	H	H
IIA-48	Phenyl	Me	H	OMe	H	H	H
IIA-50	Phenyl	Me	H	CO_2Me	H	H	H
IIA-52	Phenyl	Me	H	H	H	H	H
IIA-64	Phenyl	Me	H	H	CO_2Me	H	H
IIA-67	Phenyl	Me	H	CN	H	H	H
IIA-68	Phenyl	Me	H	H	CN	H	H
IIA-98	Phenyl	Me	H	H	NMe_2	H	H
IIA-99	Phenyl	Me	H	NO_2	H	H	H
IIA-100	Phenyl	Me	H	NHAc	H	H	H
IIA-101	Phenyl	Me	H	NH_2	H	H	H
IIA-132	Phenyl	Me					
IIA-133	Phenyl	Me					
IIA-134	Phenyl	Me	H	CH_2OH	H	H	H
IIA-135	Phenyl	Me					

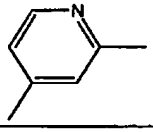
Atty. Docket No.: VPI/99-109 DIV US
Application No.: 10/779,532
Applicants: Green et al.

(b) a compound of formula  :

wherein G, A and R^1 are defined as

No.	G	A	R^1
IIAA-1	Phenyl	CH	
IIAA-2	Phenyl	CH	
IIAA-39	Phenyl	CH	
IIAA-40	Phenyl	CH	

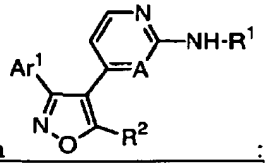
(c) a compound of formula  :



wherein Q is and

Ar^1, R^2, R^3, R^4, R^5 and R^6 are defined as

No.	Ar^1	R^2	R^3	R^4	R^5	R^6
IIIA-77	phenyl	H	COMe	H	H	H
IIIA-78	phenyl	H	CN	H	H	H

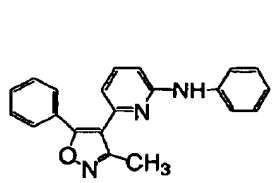
(d) a compound of formula  :

wherein Ar^1, A, R^1 and R^2 are defined as

Atty. Docket No.: VPI/99-109 DIV US
Application No.: 10/779,532
Applicants: Green et al.

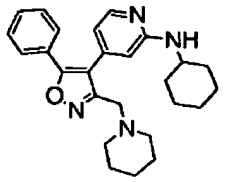
No.	Ar^1	A	R^1	R^2
XIA-1	phenyl	CH	phenyl	CH_2(morpholin-4-yl)
XIA-2	phenyl	CH	phenyl	$CH_2N(CH_3)_2$
XIA-3	phenyl	CH	phenyl	CH_2NEt_2
XIA-4	phenyl	CH	phenyl	$CH_2N(CH_3)CH_2Ph$
XIA-5	phenyl	CH	phenyl	CH_2(1-t-butoxycarbonylpiperazin-4-yl)
XIA-6	phenyl	CH	benzyl	CH_2(morpholin-4-yl)
XIA-7	phenyl	CH	cyclohexyl	CH_2(morpholin-4-yl)
XIA-8	phenyl	CH	4-[1,2-$(OMe)_2$-phenyl]	CH_2(morpholin-4-yl)
XIA-9	phenyl	CH	4-cyclohexanol	CH_2(morpholin-4-yl)
XIA-10	phenyl	CH	phenyl	$CH_2N(CH_3)CH_2CH_2N(CH_3)_2$
XIA-11	phenyl	CH	phenyl	$CH_2N(CH_3)CH_2CO_2CH_3$
XIA-12	phenyl	CH	phenyl	CH_2(piperazin-1-yl)
XIA-15	4-F-phenyl	CH	cyclohexyl	CH_2O(tetrahydrofuran-3-yl)
XIA-16	4-F-phenyl	CH	3-cyanophenyl	CH_2O(tetrahydrofuran-3-yl)
XIA-17	4-F-phenyl	CH	2-(2-pyridinyl)ethyl	CH_2O(tetrahydrofuran-3-yl)
XIA-18	4-F-phenyl	CH	1-benzyl-piperidin-4-yl	CH_2O(tetrahydrofuran-3-yl)
XIA-19	4-F-phenyl	CH	4-cyclohexanol	$CH_2OCH_2CH_2OCH_3$
XIA-20	4-F-phenyl	CH	cyclohexyl	$CH_2OCH_2CH_2OCH_3$
XIA-21	4-F-phenyl	CH	2-(2-pyridinyl)ethyl	$CH_2OCH_2CH_2OCH_3$
XIA-22	4-F-phenyl	CH	1-benzyl-piperidin-4-yl	$CH_2OCH_2CH_2OCH_3$
XIA-23	4-F-phenyl	CH	4-cyclohexanol	CH_2(morpholin-4-yl)
XIA-24	4-F-phenyl	CH	cyclohexyl	CH_2(morpholin-4-yl)
XIA-25	4-F-phenyl	CH	3-cyanophenyl	CH_2(morpholin-4-yl)
XIA-26	4-F-phenyl	CH	2-(2-pyridinyl)ethyl	CH_2(morpholin-4-yl)
XIA-27	4-F-phenyl	CH	1-benzyl-piperidin-4-yl	CH_2(morpholin-4-yl)
XIA-28	4-F-phenyl	CH	4-cyclohexanol	CH_2OCH_3
XIA-29	4-F-phenyl	CH	cyclohexyl	CH_2OCH_3
XIA-30	4-F-phenyl	CH	3-cyanophenyl	CH_2OCH_3
XIA-31	4-F-phenyl	CH	2-(2-pyridinyl)ethyl	CH_2OCH_3
XIA-32	4-F-phenyl	CH	1-benzyl-piperidin-4-yl	CH_2OCH_3
XIA-33	4-F-phenyl	CH	4-cyclohexanol	CH_2OCH_3
XIA-34	4-F-phenyl	CH	cyclohexyl	CH_2OCH_3
XIA-35	4-F-phenyl	CH	3-cyanophenyl	CH_2OCH_3
XIA-36	4-F-phenyl	CH	2-(2-pyridinyl)ethyl	CH_2OCH_3
XIA-37	4-F-phenyl	CH	4-cyclohexanol	CH_2O(tetrahydrofuran-3-yl)
XIA-38	4-F-phenyl	CH	cyclohexyl	CH_2O(tetrahydrofuran-3-yl)
XIA-41	4-F-phenyl	CH	4-methoxybenzyl	CH_2OCH_3

(e) a compound selected from:

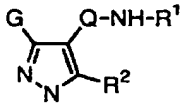


IB-3

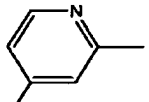
or



IB-24;

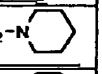
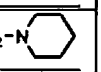


(f) a compound having the formula :



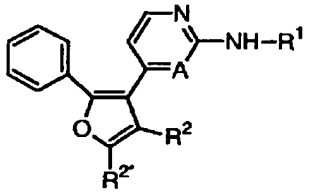
wherein Q is and

G, R^1 and R^2 are defined as

No.	G	R^1	R^2
IC-1	4-F-phenyl	Phenyl	H
IC-2	4-F-phenyl	Cyclohexyl	H
IC-3	4-F-phenyl	Isoquinolin-4-yl	H
IC-4	4-F-phenyl	6-MeO-naphthalen-2-yl	H
IC-5	4-F-phenyl	4-cyclohexanol	H
IC-9	4-F-phenyl	Cyclohexyl	CH_3
IC-10	4-F-phenyl	Cyclohexyl	
IC-11	Phenyl	Cyclohexyl	

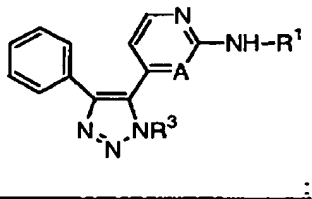
and

(g) a compound of formulae:



ID

or



IE

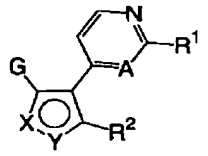
wherein R^1 is phenyl, $R^{2'}$ is hydrogen and A is CH, and

R^2 is H or CH_3 in formula ID; or

R^3 is H or CH_3 in formula IE.

9. (Canceled).

10. (Currently amended) A compound having the formula:



wherein:

X-Y is N-O or O-N ~~providing an isoxazole or reverse isoxazole ring~~;

A is ~~N or~~ CH;

G is R, aryl or substituted aryl;

R is aliphatic or substituted aliphatic;

R^2 is selected from hydrogen, -R, $-CH_2OR$, $-CH_2OH$, -CH=O, $-CH_2SR$, $-CH_2S(O)_2R$, $-CH_2(C=O)R$, $-CH_2CO_2R$, $-CH_2CO_2H$, $-CH_2CN$, $-CH_2NHR$, $-CH_2N(R)_2$, -CH=N-OR, -CH=NNHR, $-CH=NN(R)_2$, -CH=NNHCOR, $-CH=NNHCO_2R$, $-CH=NNHSO_2R$, -aryl, -substituted aryl, $-CH_2$(aryl), $-CH_2$(substituted aryl), $-CH_2NH_2$, $-CH_2NHCOR$, $-CH_2NHCONHR$, $-CH_2NHCON(R)_2$, $-CH_2NRCOR$, $-CH_2NHCO_2R$, $-CH_2CONHR$, $-CH_2CON(R)_2$, $-CH_2SO_2NH_2$, $-CH_2$(heterocyclyl), $-CH_2$(substituted heterocyclyl), -(heterocyclyl), or -(substituted heterocyclyl)~~; and~~

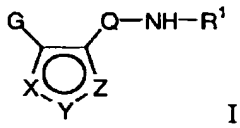
R^1 is ~~selected from halogen,~~ NH_2~~, SR, or SO_2R~~;

~~provided that R^1 is other than Br or Cl when A is CH~~.

11. (Original) A pharmaceutical composition comprising an amount of a compound according any one of claims 1-8 effective to inhibit JNK, and a pharmaceutically acceptable carrier.

Atty. Docket No.: VPI/99-109 DIV US
Application No.: 10/779,532
Applicants: Green et al.

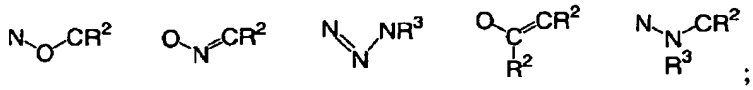
12. (Currently amended) A method for treating a disease state or condition in mammals that is alleviated by treatment with a protein kinase inhibitor, comprising administering to a mammal in need of such a treatment a therapeutically effective amount of a compound of formula I:



I

wherein:

X-Y-Z is selected from one of the following:



;

R^1 is H, $CONH_2$, $T_{(n)}$-R, or $T_{(n)}$-Ar^2;

R is an aliphatic or substituted aliphatic group;

n is zero or one;

T is C(=O), CO_2, CONH, $S(O)_2$, $S(O)_2NH$, $COCH_2$ or CH_2;

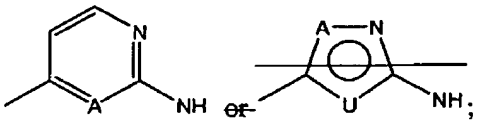
each R^2 is independently selected from hydrogen, -R, $-CH_2OR$, $-CH_2OH$, -CH=O, $-CH_2SR$, $-CH_2S(O)_2R$, $-CH_2(C=O)R$, $-CH_2CO_2R$, $-CH_2CO_2H$, $-CH_2CN$, $-CH_2NHR$, $-CH_2N(R)_2$, -CH=N-OR, -CH=NNHR, $-CH=NN(R)_2$, -CH=NNHCOR, $-CH=NNHCO_2R$, $-CH=NNHSO_2R$, -aryl, -substituted aryl, $-CH_2$(aryl), $-CH_2$(substituted aryl), $-CH_2NH_2$, $-CH_2NHCOR$, $-CH_2NHCONHR$, $-CH_2NHCON(R)_2$, $-CH_2NRCOR$, $-CH_2NHCO_2R$, $-CH_2CONHR$, $-CH_2CON(R)_2$, $-CH_2SO_2NH_2$, $-CH_2$(heterocyclyl), $-CH_2$(substituted heterocyclyl), -(heterocyclyl), or -(substituted heterocyclyl);

each R^3 is independently selected from hydrogen, R, COR, CO_2R or $S(O)_2R$;

G is R or Ar^1;

Ar^1 is aryl, substituted aryl, aralkyl, substituted aralkyl, heterocyclyl, or substituted heterocyclyl, wherein Ar^1 is optionally fused to a partially unsaturated or fully unsaturated five to seven membered ring containing zero to three heteroatoms;

Q-NH is



wherein the H of Q-NH is optionally replaced by R^3;

A is ~~N or~~ CR^3;

~~U is CR^3, O, S, or NR^3;~~

Ar^2 is aryl, substituted aryl, heterocyclyl or substituted heterocyclyl, wherein Ar^2 is optionally fused to a partially unsaturated or fully unsaturated five to seven membered ring containing zero to three heteroatoms;

wherein each substitutable carbon atom in Ar^2, including the fused ring when present, is optionally and independently substituted by halo, R, OR, SR, OH, NO_2, CN, NH_2, NHR, $N(R)_2$, NHCOR, NHCONHR, $NHCON(R)_2$, NRCOR, $NHCO_2R$, CO_2R, CO_2H, COR, CONHR, $CON(R)_2$, $S(O)_2R$, $SONH_2$, S(O)R, SO_2NHR, or $NHS(O)_2R$, and wherein each saturated carbon in the fused ring is further optionally and independently substituted by =O, =S, =NNHR, $=NNR_2$, =N-OR, =NNHCOR, $=NNHCO_2R$, $=NNHSO_2R$, or =NR; and

wherein each substitutable nitrogen atom in Ar^2 is optionally substituted by R, COR, $S(O)_2R$, or CO_2R.

13. (Currently amended) The method ~~of~~ according to claim 12, wherein the disease state is alleviated by treatment with an inhibitor of JNK.

14. (Currently amended) The method ~~of~~ according to claim 12, wherein the disease is selected from inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, infectious diseases, neurodegenerative diseases, allergies, reperfusion/ischemia in stroke, heart attacks, angiogenic disorders, organ hypoxia, vascular hyperplasia, cardiac hypertrophy, thrombin-induced platelet aggregation or conditions associated with proinflammatory cytokines.

15. (Original) The method according to claim 12, wherein said method is used to treat or prevent an inflammatory disease selected from acute pancreatitis, chronic pancreatitis, asthma, allergies, or adult respiratory distress syndrome.

16. (Original) The method according to claim 12, wherein said method is used to treat or prevent an autoimmune disease selected from glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, multiple sclerosis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, psoriasis, or graft vs. host disease.

17. (Original) The method according to claim 12, wherein said method is used to treat or prevent a destructive bone disorders selected from osteoarthritis, osteoporosis or multiple myeloma-related bone disorder.

18. (Original) The method according to claim 12, wherein said method is used to treat or prevent a proliferative disease selected from acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, or multiple myeloma.

19. (Original) The method according to claim 12, wherein said method is used to treat or prevent neurodegenerative disease selected from Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, cerebral ischemia or neurodegenerative disease caused by traumatic injury, glutamate neurotoxicity or hypoxia.

20. (Original) The method according to claim 12, wherein said method is used to treat or prevent ischemia/reperfusion in stroke or myocardial ischemia, renal ischemia, heart attacks, organ hypoxia or thrombin-induced platelet aggregation.

21. (Original) The method according to claim 12, wherein said method is used to treat or prevent a condition associated with T-cell activation or pathologic immune responses.

22. (Original) The method according to claim 12, wherein said method is used to treat or prevent an angiogenic disorder selected from solid tumors, ocular neovasculization, or infantile haemangiomas.

23. (Currently amended) The method ~~of~~ according to claim 12, wherein the disease state or condition is alleviated by treatment with an inhibitor of a Src-family kinase.

24. (Currently amended) The method ~~of~~ according to claim 12, wherein the disease state or condition is hypercalcemia, restenosis, hypercalcemia, osteoporosis, osteoarthritis, symptomatic treatment of bone metastasis, rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, psoriasis, lupus, graft vs. host disease, T-cell mediated hypersensitivity disease, Hashimoto's thyroiditis, Guillain-Barre syndrome, chronic obtructive pulmonary disorder, contact dermatitis, cancer, Paget's disease, asthma, ischemic or reperfusion injury, allergic disease, atopic dermatitis, or allergic rhinitis.